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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/629,318	07/28/2003	Andrew P. Feinberg	JHU1900-1	6572

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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/629,318	FEINBERG, ANDREW P.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *9,12 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,11 and 13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1203;0105;07063*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-20, and of the species of primer pair SEQ ID NO 23-24 in the reply filed on April 26, 2006 is acknowledged. The traversal is on the ground(s) that the examination of Groups I-II together would not impose a serious burden. This is not found persuasive because Groups I-II require different searches and a review of different types of prior art references. For example, a search of Group II would require a search for any prior art molecules including SEQ ID Nos 23 and 24, as the kits of Group II do not require the use of the primers in particular method steps. In contrast, a search of Group I requires a search of a variety of particular method steps, but only requires consideration of primers to the extent that they may have been disclosed for use in methods meeting the requirements of the invention of Group I.

The requirement is still deemed proper and is therefore made FINAL.

2. Claim 21 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Further, claims 9 and 12, which are drawn to non-elected primer combinations, are also withdrawn. Applicant timely traversed the restriction (election) requirement in the reply filed on April 26, 2006. Claims 1-8, 10-11 and 13-20 are considered herein. It is noted that as a teaching of methods employing the elected primer pair 23-24 and otherwise meeting the limitations claim 8 was not identified in the prior art, the examiner

search was extended to additional species in order to complete the examination of claim 8.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-8, 10-11, and 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 are indefinite because while the claims are drawn to a method "for identifying loss of imprinting of the IGF2 gene," the method steps of the claims do not refer to LOI or indicate how LOI is actually detected. Clarification is required.

Similarly, claims 10-11 and 13-16 are indefinite because while the claims are drawn to a method "for identifying an increased risk of developing cancer," the method steps of the claims do not refer to cancer or indicate how cancer is actually detected. Clarification is required.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-4, 10, 13-17, and 19-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Ahomadegbe et al (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 37, p. 598 [April 1996]).

Ahomadegbe et al disclose the detection of both loss of imprinting and hypomethylation of the H19 and IGF2 genes in two types of invasive breast carcinomas (see entire abstract). With further regard to claims 10 and 17 and claims dependent therefrom, it is further noted that the reference teaches that LOI was absent in 15 normal breast tissue samples and present in both non inflammatory and inflammatory breast cancer samples, and that the reference further suggests that H19 and IGF2 status may be associated with tumor aggressiveness. Regarding claims 2-3, 14, and 20, it is noted that while Ahomadegbe et al do not disclose the sequences of the genes they analyzed, the claims as written encompass sequences that include any "fragment" of SEQ ID NOS 1 or 6; as a single nucleotide constitutes a fragment, the molecules analyzed by Ahomadegbe et al meet the requirements of the claims. Regarding claim 13, it is noted that the subjects analyzed by Ahomadegbe et al are not disclosed as being "known to have a colorectal neoplasm." Regarding claim 16, Ahomadegbe et al disclose the analysis of lymphocytes.

7. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Ahomadegbe et al, as evidenced by Moore (GenBank Accession No. Y13633 [12/1997]).

The teachings of Ahomadegbe et al are set forth in paragraph 6 above. Ahomadegbe et al teach that they analyzed both the human IGF2 and H19 genes for hypomethylation; however, the reference does not disclose the nucleotide sequences of

the genes analyzed. Moore teaches the sequence of exon 3 of the human IGF2 gene, of which nucleotides 661-916 are 100% identical to instant SEQ ID NO: 1. As the nucleotide sequence of the IGF2 gene is an inherent property of the gene, the Ahomadegbe et al reference inherently teaches analysis of a sequence that includes the sequence of instant SEQ ID NO: 1. Accordingly, Ahomadegbe et al anticipate claim 8. Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Ahomadegbe et al, as evidenced by Ishihara et al (GenBank Accession No. AF087017 [10/1998]).

It is first noted that a review of the revision history of GenBank Accession No. AF087017 (attached to the sequence alignment enclosed herewith) establishes that the nucleotide sequence corresponding to the Accession number has not changed since October 1998.

The teachings of Ahomadegbe et al are set forth in paragraph 6 above. Ahomadegbe et al teach that they analyzed both the human IGF2 and H19 genes for hypomethylation; however, the reference does not disclose the nucleotide sequences of the genes analyzed. Ishihara et al teach the sequence of the human H19 gene, of which nucleotides 2057-8070 are 100% identical to instant SEQ ID NO: 6. As the nucleotide sequence of the H19 gene is an inherent property of the gene, the Ahomadegbe et al reference inherently teaches analysis of a sequence that includes the sequence of instant SEQ ID NO: 6. Accordingly, Ahomadegbe et al anticipate claim 6.

9. Claims 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Cui et al (Nature Medicine 4(11):1276-1280 [11/1998][cited in the IDS of 01/2005).

Cui et al teach the detection of LOI of the IGF2 gene in tumor and matched normal samples obtained from colorectal cancer patients (see entire reference). Cui et al teach that LOI "was specifically associated with MSI [microsatellite instability] in colorectal cancer," and also state that patients in the general population exhibiting LOI "may have cancer or be at increased risk for cancer" (see page 1279). The methods of Cui et al therefore meet the limitations of claim 17-18.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ahomadegbe et al in view of Takai et al (Human Molecular Genetics 10(23):2619-2626 [2001][cited in the IDS of 12/2003]).

Ahomadegbe et al disclose the detection of both loss of imprinting and hypomethylation of the H19 and IGF2 genes in two types of invasive breast carcinomas (see entire abstract). However, Ahomadegbe et al do not teach the analysis of an H19 gene DMR that comprises a CTCF binding site, as required by the claim. Takai et al teach that the promoter of the human H19 includes 7 potential CTCF-binding sites, teaches analysis of these sites for hypomethylation, and teaches that hypomethylation of the sixth such site is associated with human bladder cancer (see entire reference, particularly page 2620, right column). In view of the teachings of Takai et al, it would

have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ahomadegbe et al so as to have analyzed the samples of Ahomadegbe et al for hypomethylation at the specific CTCF binding sites taught by Takai et al. An ordinary artisan would have been motivated to have much such a modification so as to have established which sites within the H19 gene were hypomethylated in breast cancer and thus most informative with regard to cancer detection.

12. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ahomadegbe et al in view of Cui et al (Cancer Research 61:4947-4950 [7/1/2001][cited in the IDS of 12/2003]).

Ahomadegbe et al disclose the detection of both loss of imprinting and hypomethylation of the H19 and IGF2 genes in two types of invasive breast carcinomas (see entire abstract). However, Ahomadegbe et al do not disclose what particular methods were used to detect methylation status of these genes. Cui et al disclose the use of bisulfite genomic sequencing to determine H19 methylation, and report the use of primers corresponding to SEQ ID NOS 7-21 and 31-34 in their methods (see the disclose of primers for sequences H1-H8 in Table 1, corresponding in order to instant SEQ ID NOS 7-21, and of the 4 primers disclosed at the bottom of the left column on page 4948, which correspond in order to instant SEQ ID NOS 31-34). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ahomadegbe et al so as to have employed the methods and primers of Cui et al in detection of H19 methylation status. As Cui et al

provide specific guidance with regard to how their primers may be employed in detecting methylation status of H19, an ordinary artisan would have been motivated to have used the prior art methods and primers of Cui et al, rather than, e.g., to have performed experimentation aimed at identifying a satisfactory method of detecting H19 methylation status, for the advantages of saving time and reagents and more rapidly achieving the goal of detecting hypomethylation.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 17-18 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14, 16-20, and 23-42 of copending Application No. 10/336,552. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

The instant claims merely require a method "for identifying an increased risk of developing cancer" in which a biological sample from the subject is analyzed for LOI of the IGF2 gene, wherein LOI is indicative of increased risk. While the '552 claims include additional limitations and are more specific than the instant claims, the '552 claims also encompass methods in which IGF2 gene LOI is detected as an indicator of increased risk of cancer (including colorectal cancer). Thus, the '552 claims anticipate the instant claims, and the '552 claims and the instant claims are not patentably distinct from one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Diana B Johannsen

Diana B. Johannsen
Primary Examiner
Art Unit 1634